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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/855,797	05/16/2001	James L. Hartley	0942.285000G	2106

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EXAMINER	
LEFFERS JR, GERALD G	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 04/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/855,797	HARTLEY ET AL.	
	Examiner	Art Unit	
	Gerald G. Leffers Jr., PhD	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *52-59 and 61-78* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *52-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *5/16/01 & 10/6/03* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/1/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

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DETAILED ACTION

Response to Amendment

Receipt is acknowledged of an amendment, filed 2/1/2005, in which claim 60 was cancelled and in which new claims 70-78 were added.

Any rejection of record in the instant application not addressed herein is withdrawn. A new rejection is made herein with regard to the metes and bounds of the term recombination site. This action is not final as the new grounds of rejection made herein were not necessitated by applicants' amendment to the claims in the response filed 2/1/2005.

Information Disclosure Statement

Receipt is acknowledged of a pair of information disclosure statements (IDS's) filed 2/1/2005. The signed and initialed PTO Form 1449's has been mailed with the instant action.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The rejected claims are directed to *in vitro* methods for synthesizing one or more nucleic acid molecules comprising one or more recombination sites. The methods comprise 1) obtaining at least one isolated linear nucleic acid molecule, 2) contacting the molecule with one or more adapters comprising a first recombination site or portions thereof under conditions sufficient to

add one or more of said adapters to one or more termini of the linear nucleic acid molecule, and 3) mixing the linear nucleic acid molecule with at least one vector *in vitro* in the presence of at least one recombination protein under conditions sufficient to cause recombination of the linear nucleic acid molecule with the vector.

The instant specification defines recombination proteins at page 23, lines 25-27: "Recombination proteins[:] include excisive or integrative proteins, enzymes, co-factors or associated proteins that are involved in recombination reactions involving one or more recombination sites. See Landy (1994), *infra*." The specification does not explicitly define the term "recombination site", allowing the skilled artisan to interpret the term broadly to include any site within a nucleic acid that allows it to recombine with a heterologous nucleic acid molecule. The definition provide by the instant specification for the term is at page 29, lines 5-9: "Adapter: is an oligonucleotide or nucleic acid fragment or segment (preferably DNA) which comprises one or more recombination sites (or portions of such recombination sites) which in accordance with the invention can be added to a circular or linear Insert Donor molecule as well as other nucleic acid molecules described herein." Given a reasonably broad interpretation of the claim limitations, the rejected claims read on any cloning methodology featuring the use of a linear DNA substrate (e.g. a phage genomic DNA) for PCR amplification with primers (i.e. adapters) comprising sequences that can be used to insert the amplified DNA into a vector (e.g. restriction enzyme sites) and subsequent insertion of the amplified insert DNA into a recombination vector.

Claims 52-59, 61-63, 66-78 are rejected under 35 U.S.C. 102(b) as being anticipated by Bebee et al (U.S. Patent No. 5,434,066; of record; see the entire patent). **This rejection is maintained for reasons of record, which are reiterated below, and is extended to new claims 70-78.**

Bebee et al teach the generation of several different vectors where desired sequences were obtained from the phage P1 genome (e.g. P1 vir phage used as a source of genomic DNA) via PCR amplification (Examples 1-2, columns 11-12). For example, the incA region of P1 was amplified from phage P1 vir genomic DNA and subsequent insertion into the BspHI site of vector pSPORT1 (e.g. Example 3). In this example, the "recombination protein" is the ligase used to join a linear fragment of DNA comprising adapters at either terminus that in turn comprise "at least a portion of" a recombination site (e.g. *any* dinucleotide sequence found in *any* given recombination site) with a vector nucleic acid in an *in vitro* reaction mixture. Bebee further teaches an example where a HeLa cDNA library is cloned into a vector (pZipLox) via Not I and Sal I sites on the vector (e.g. Examples 3 & 4). The examiner knows of no other way to generate a library of cDNAs where each cDNA comprises Not I and Sal I sites unless "adapters" comprising the restriction sites were introduced into the cDNA products.

Response to Arguments

Applicant's arguments filed in the response filed 2/1/2005 have been fully considered but they are not persuasive. The response essentially argues that Bebee et al do not teach *in vitro* recombination of the DNA substrates. For example, the response essentially argues that the pZL plasmid is generated by *in vivo* recombination mediated by the Cre recombinase between LoxP sites on a closed circular DNA susbstrate (i.e. pSAX10). These are a repeat of previous

arguments. The response further argues that the amendment of claim 52 to recite that the vector comprises a second recombination site and that recombination occurs between those sites obviates the rejection with regard to claim 52 and its dependent claims. It is asserted that the amendment to claim 69 to specify that the at least first recombination site, or portions thereof, is an att site or mutants or variants thereof necessarily obviates the grounds of rejection. Finally, it is asserted that the examiner's interpretation of the term "recombination site" is inconsistent with both the instant application and the ordinary meaning of the term.

To the extent that the applicants' previous arguments concerning the meaning of the term "recombination site", the examiner's previous response to these arguments is incorporated here by reference. Although it is a moot point, the examiner respectfully points out that the citation provided by applicant (column 12, lines 58-62) does not clearly indicate that recombination of the linear insert with the vector to produce pZL necessarily occurred *in vivo*. The cited passage merely indicates that Kanamycin-sensitive clones were isolated after transformation of *E. coli* cells. There is no indication that recombination necessarily occurred *in vivo*.

In any case, the issue here appears to be the metes and bounds of the term "recombination site". Applicants' assertion that the ordinary meaning of the word "recombination site" is synonymous with "site-specific recombination site" is unsupported. The term "recombination site" is not synonymous with the term "site-specific recombination site". For example, there were numerous ways known in the art at the time of filing in which nucleic acids can be "recombined". For example, one could mediate recombination at a desired site using short regions of homology. Alternatively, one could use blunt-end ligation to mediate the desired recombination. In each case, the site of recombination two different nucleic acid molecules can

be considered a "recombination site". While it is understood that applicants can be their own lexographer, at no point in the instant application is the term "recombination site" unambiguously defined as being limited to a "site-specific" recombination site. This ambiguity as to what is conveyed to the skilled artisan is compounded by the use of terms like "portion thereof" or "mutants or variants thereof" in reference to the recombination sites. The terms are not explicitly defined in the instant specification in any limiting way and are open to interpretation. As such, the claims comprising these terms read on as little as even a single nucleotide from a given recombination site (e.g. a "mutant" or "variant" of an *att* site).

It is again noted that there is no limitation in the rejected claims that the recombination protein is a site-specific recombinase (e.g. Cre, Int, Xis, etc.) or even that the recombination is mediated by the recombination protein that is explicitly recited in the claims. Applicants are attempting to distinguish themselves from the prior art by asserting a definition for the term "recombination site" that is not consistent with the ordinary meaning of the term for one of skill in the art. It would be remedial to amend the claims to specifically recite that (i) the recombination site is a site-specific recombination site, and (ii) that the recombination is mediated by a site-specific recombinase.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

Claims 52-59, 61-78 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Each of the rejected claims recites the limitations of a "recombination site" and/or "recombination protein". **This is a new rejection.**

Applicants are attempting to distinguish themselves from the prior art based upon an interpretation of these terms that is contrary to the ordinary usage in the art. Applicants assert that the term "recombination site" is, in view of the specification, necessarily synonymous with the term "site-specific recombination site". This is inaccurate. The term is never defined in the instant specification as being limited to a site recognized by site-specific recombinase proteins. Further, the term "recombination site" can encompass recombination mechanisms that are mediated by a number of enzymes that are not site-specific recombinases (e.g. ligases, homologous recombination proteins such as RecA, restriction enzymes, etc.). The instant specification does define recombination proteins at page 23, lines 25-27: "Recombination proteins[:] include excisive or integrative proteins, enzymes, co-factors or associated proteins that are involved in recombination reactions involving one or more recombination sites. See Landy (1994), *infra*." This definition for recombination protein is broader than what is actually exemplified in the instant specification. Thus, because the terms "recombination site" and "recombination protein" can be interpreted more broadly than what is actually exemplified in the specification, it is not clear from the specification that the terms "recombination site" and "recombination protein" are necessarily limited to site-specific recombinase sites and site-

specific recombinases, respectively. Therefore, the metes and bounds of what is claimed are unclear.

Claim 52 is vague and indefinite in that it is unclear the nature of the "conditions sufficient to cause recombination of said linear nucleic acid molecule with said vector". **This rejection is maintained for reasons of record, which are repeated below.**

As written, the claim encompasses embodiments wherein the recombination reaction between the vector and linear nucleic acid is not mediated by the recombination protein that is explicitly recited in the claims or that the recombination necessarily occurs via the recombination site or sites provided by the one or more adapters. Upon reading the specification, however, the invention appears to be that the *in vitro* recombination reaction necessarily occurs via the action of the recombination protein that is explicitly recited in the claims via the recombination sites provided by the adapter or adapters present on the ends of the linear DNA. If the recombination does not proceed via the explicitly recombination protein and recombination sites, what then are the conditions suitable for recombination between the linear DNA fragment and the vector? In the absence of disclosure of such conditions in the instant specification, the metes and bounds of such conditions cannot be clearly determined.

Response to Arguments

Applicant's arguments filed in the response filed 2/1/2005 have been fully considered but they are not persuasive. The response essentially argues that the ordinarily skilled artisan would readily recognize that the recited method requires the interaction between the recombination site(s) on the linear nucleic acid molecules and the recombination site(s) on the vector, in the presence of the recombination protein, such that a recombination reaction occurs between the

two sites. The response further argues that the phrase "conditions sufficient to cause recombination" are well known to those skilled in the art, particularly in light of the instant specification (e.g. the working examples).

The implied assertion that the skilled artisan would necessarily realize that "conditions sufficient to cause recombination between the two sites" and in the presence of the recombination protein would mean that the recited recombination protein necessarily mediates the recombination reaction. This is not accurate. There is no explicit limitation in the rejected claims that the recited recombination protein mediates the recombination event. As indicated above, there are numerous ways in which "recombination sites" can be joined (e.g. ligation, blunt-ended ligation, homologous recombination, illegitimate recombination, etc.). Therefore, the metes and bounds of the phrase "conditions sufficient to cause recombination" remain unclear.

Conclusion

No claims are allowed. Claim 64 is objected to as being dependent upon a rejected claim but would be free of the art if rewritten as an independent claim comprising each of the limitations of the claim(s) upon which it is currently dependent. Claim 64 is also rejected under 35 U.S.C. 112 2nd paragraph.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald G. Leffers Jr., PhD whose telephone number is (571) 272-0772. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gerald G Leffers Jr., PhD
Primary Examiner
Art Unit 1636

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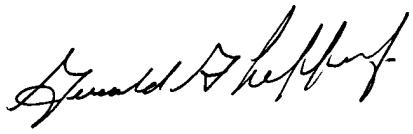

GERRY LEFFERS
PRIMARY EXAMINER